Cell Host & Microbe
Previews

The Mycobiome: Influencing IBD Severity

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DOI 10.1016/j.chom.2012.05.009

The etiology and maintenance of inflammatory bowel disease (IBD) is the subject of much speculation. Iliev et al. (2012) impose a change in our views of the gut microbiome and catapult the fungal "mycobiome" center-stage in the exploration of IBD.

The interaction between a host and its microbiome is essential for health of the host organism (Figure 1). However, recent investigations have been mostly limited to studying commensal bacteria, with fungi largely being ignored as constituents of the host microbiota. Indeed, the idiom "microbiome" has become synonymous with commensal bacteria. Key among investigations of the interactions between the microbiome and the host has been identifying the role played by these microbes in the etiology and maintenance of inflammatory bowel disease (IBD). It has now been established that alterations in the bacterial population can lead to gut inflammation (Willing et al., 2010), but the presence and role of fungi in these processes is unknown. Although the presence of a commensal fungal community on mucosal surfaces has been posited, little has been done to investigate the influence of these microbes on health and disease and, to date, only an oral "mycobiome" has been characterized (Ghannoum et al., 2010).

A recent study by Iliev et al. (2012) identified that a populous gut mycobiome exists in several mammalian species. This community showed reactivity with Dectin-1, the host pattern recognition receptor (PRR) for β-glucan, and demonstrated varied morphologies. Genomic characterization of the murine gut mycobiome indicated that it is a varied "multiethnic" community of diverse fungal species. Like any such population, the mycobiome was not homogenous but, surprisingly, over 97% of the population comprised just ten fungal species and remarkably, a single dimorphic fungus, *Candida tropicalis*, constituted over 65% of the entire population. By comparing these fungal species to those detected in mouse food, the authors confirmed that the vast majority of these fungi are indigenous to the gut, rather than food passengers. These findings are notable, as they show that *Candida spp.* are a major part of the mammalian gut mycobiome, although interestingly in humans it would appear that *C. albicans* and *C. parapsilosis* are the major fungal constituents (Scanlan and Marchesi, 2008). Indeed, *C. albicans* is not a natural colonizer of mice, although the reasons for this are still unclear.

Next, Iliev et al. (2012) addressed the effects this mycobiome has on general host health and reason with some justification that if gut commensal fungi are recognized by Dectin-1, then mice deficient in this receptor may show differences in susceptibility to IBD. As predicted, Dectin-1-deficient (*Clec7a*$^{-/-}$) mice suffered greater severity of symptoms in a dextran sulfate sodium (DSS)-induced colitis model, demonstrating increased weight loss, histological changes, and proinflammatory cytokine production. This was not due to differences in commensal bacteria between the wild-type and *Clec7a*$^{-/-}$ mice, as the microbiota was the same in both strains. The intriguing question here is whether this increased sensitivity is driven solely by Dectin-1 deficiency or by an altered microbiota *Clec7a*$^{-/-}$ mice, as has been reported in NLRP6$^{-/-}$ mice (Elinav et al., 2011). To answer this, the authors used a fecal transplant from *Clec7a*$^{-/-}$ to wild-type mice, with the recipient animals showing no increase in sensitivity to DSS colitis. Thus, the increased sensitivity appears to be due to the lack of Dectin-1 function rather than an altered microbiota.

The authors next investigated what happens to the mycobiome during the course of gut inflammation. It has been well documented that gut inflammation drives changes in the gut bacterial population (Willing et al., 2010), so the authors assumed that similar changes may occur in the mycobiome. As predicted, there was an overall increase in "opportunistic pathogenic" fungi (*Candida, Trichosporon*) and a decrease in nonpathogenic fungi (*Saccharomyces*). Concurrent with this shift, there is evidence of fungal invasion of inflamed tissues in DSS-treated *Clec7a*$^{-/-}$ mice, whereas in DSS-treated wild-type mice the fungi are restricted to the lumen, suggesting Dectin-1 plays a role in preventing fungi from breaching the mucosal barrier and gaining entry to the host all-you-can-eat buffet. The notion that this is a host-mediated event rather than a change in microbiota gains further support from the authors' observation that gut-conditioned dendritic cells from *Clec7a*$^{-/-}$ mice are restricted in their ability to kill *C. tropicalis* in vitro. Furthermore, gut administration of *C. tropicalis* to *Clec7a*$^{-/-}$ mice results in more severe DSS-induced colitis with all its ancillary pathology. Wild-type mice showed no effects beyond the norm. Notably, treatment of *Clec7a*$^{-/-}$ mice with an antifungal drug during colitis reversed these effects. It will be interesting to see if this effect is common to all pathogenic, filamentous fungi and whether all nonpathogenic fungi are incapable of inducing these responses, thus identifying if this is a common fungal effect or specific to *Candida* species. Taken together, these data suggest that Dectin-1 deficiency leads to altered immunity to commensal fungi in the gut. Further, they indicate the paramount importance of epithelial cells and epithelium integrity in maintaining health, as it is only when this barrier is perturbed that Dectin-1 deficiency becomes important and affects inflammatory disease severity.

A key question is whether these observations in mice equate to a similar role for Dectin-1 in human disease. To address

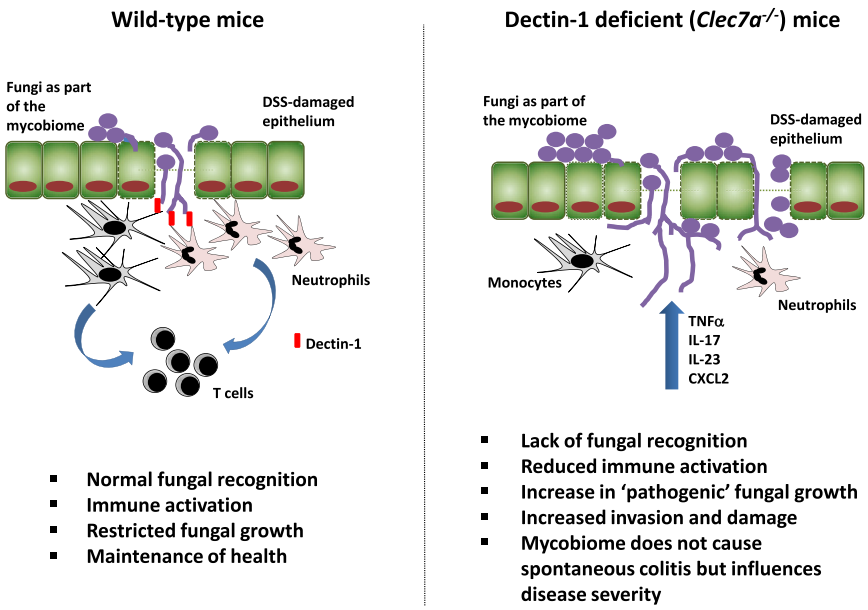

Figure 1. The Mycobiome and Gut Inflammation

Interactions between fungi in the mycobiome and host cells in the gut affect how inflammatory diseases progress. Breaches in the epithelial barrier due to localized inflammation allow fungi from the mycobiome to invade the underlying tissue, exposing them to immune cells. In wild-type gut, this contact triggers immune recognition of fungi via the Dectin-1 receptor, resulting in activation of antifungal responses and restriction in fungal growth. In contrast, Dectin-1-deficient (Clec7a$^{-/-}$) gut has a reduced ability to recognize and respond to fungi, allowing them to invade more extensively without restriction. This results in increased damage leading to increased inflammation, exacerbating the symptoms of inflammatory bowel disease.

this, the authors compared the sequence of the human Dectin-1 gene (*CLEC7A*) between a group of severe, medically refractive ulcerative colitis (MRUC) patients and another less severe group (non-MRUC). In doing so, they identified a single nucleotide polymorphism (SNP) associated with MRUC and a two-SNP haplotype even more strongly associated with MRUC. Future studies should aim to determine the effect of these haplotypes on the functional activity of Dectin-1, although one could speculate that they might lead to some loss of functionality. Given that *CLEC7A* has not been identified as an IBD susceptibility gene by any GWAS study to date, the authors propose that *CLEC7A* is a severity gene, with variants aggravating already-established disease. This fits the known phenotypes of *Clec7a*$^{-/-}$ mice, which do not develop colitis spontaneously but do suffer from a more severe form of the disease. It will be interesting in the future to see if introduction of these SNPs into the *CLEC7A* gene in mice also results in an increased severity of IBD.

These findings are an important step forward in our understanding of microbiome-host interactions. Along with other studies now being published, they represent a substantial shift in our understanding of host-microbial interactions and host-fungal interactions in particular. As we identify more receptors recognizing fungal moieties, such as Dectin-2 recognition of α-mannans (Saijo et al., 2010), and identify the cooperation between these receptors in fungal recognition (Netea et al., 2006), studies with these receptors will help to further elucidate the importance of host-fungal interactions in homeostasis and pathogenesis. A recent study has already implicated fungal cell-wall mannoproteins in *Candida glabrata*-induced colitis (Jawhara et al., 2012). It will be interesting to see how deficiencies in each of these fungal PRRs affect bowel inflammation, particularly given that the different receptors activate different "flavors" of immune response (Gringhuis et al., 2011). Looking to the future, it remains to be determined whether the role of these interactions with the host immune system (and epithelial cells) is purely a pathological process or whether they play a major role in the homeostasis and immune development of a host, as is the case for some bacteria. This is an intriguing possibility given the filamentous morphology of some fungi, in common with other gut microbiome members (notably segmented filamentous bacteria) that are suspected of "tutoring" immune responses (Ivanov and Littman, 2010). Filamentation may be a key fungal factor in penetrating the thick, mucus layer covering the gut epithelial surface, enabling continued interaction between the host and these microbes. A better understanding of how we interact with our mycobiome and what the consequences of these interactions are may well lead to a world of new and exciting possibilities.

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